Walden Inversion of Amino Acids. VI. The Synthesis of D-Surinamine (N-Methyl-D-tyrosine)

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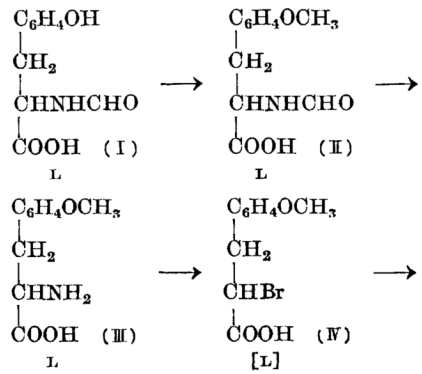
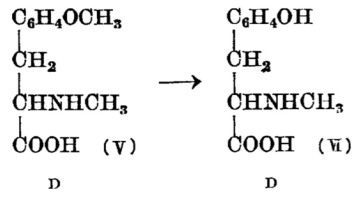
The synthesis of L-surinamine was carried out by Fischer and Lipschitz[1] from L-tyrosine through *p*-toluenesulfonyl derivatives. Recently, Corti[2] treated L-tyrosine with dimethyl sulfate and obtained L-surinamine. But no synthesis of D-surinamine has yet been attempted. The present study was undertaken to accomplish the synthesis of D-surinamine, and the reactions utilized were as follows:



(1) E. Fischer and W. Lipschitz, *Ber.*, **48**, 360 (1915).
(2) U. A. Corti, *Helv.*, **32**, 681 (1949).



One of us (N. I.) has reported the results of his studies on Walden inversion of some amino acids,[3] such as δ-benzoyl-L-ornithine, ε-benzoyl-L-lysine, L-methionine, S-methyl-L-cysteine, S-butyl-L-cysteine, S-benzyl-L-cysteine, O-methyl-L-threonine, β-methoxy-DL-norvaline and 1 (or 3)-benzyl-L-histidine, and recognized a certain regularity in the case of amination and methylamination at 0 and 100° of the [L]-α-bromo acid prepared by the action of nitrosyl bromide on L-amino acid.

O-Methyltyrosine produced by the action of ammonia on the bromo acid (IV) at 100° was racemic, but O-methyltyrosine obtained at 0° was of D-form and showed the occurrence of Walden inversion. In the case of methylamination either at 100 or 0°, the obtained O, N-dimethyltyrosine was of D-form. But it must be noted that Rivers and Lerman[4] synthesized O-methyl-D-tyrosine before we did by the reaction of ammonia on bromo acid (IV) at 0°.

Though N-formyl-L-tyrosine was synthesized by Fischer[5] in 1907, we obtained a good yield of the substance by the method of Fruton and Clarke.[6] O-Methyl-L-tyrosine had already been prepared by Behr and Clarke[7] by methylation and subsequent hydrolysis of N-acetyl-L-tyrosine, and by Rivers et al.[4] by catalytic reduction of O-methyl-N-carbobenzoxy-L-tyrosine. But, the method adopted by the present authors seems preferable to the existing methods described above in the yield and the procedure. The compound (III) had $[\alpha]_D^{17} = -5.7°$ (the authors), $[\alpha]_D^{29} = -5.9°$[7] and $[\alpha]_D^{17} = -10.0°$.[4] Therefore, it was expected that we might obtain a partly racemized product after formylation. But actually, L-tyrosine obtained by the hydrolysis of our -O methyl-L-tyrosine and D-surinamine by the methylamination of bromo acid (IV) and subsequent hydrolysis were optically pure substances.

Experimental

N-Formyl-L-tyrosine (I).—L-Tyrosine (18.1 g.), having m.p. 314~316° (decomp.) and $[\alpha]_D^{10} = -12.1°$ (c=2.81, 3N HCl), was treated with 85% formic acid (220 cc.) and acetic anhydride (65 cc.) by Fruton and Clarke's method of formylation. At the end of the reaction, the solution was evaporated under reduced pressure. An ice cold N-hydrochloric acid was added to the remaining product to dissolve tyrosine not reacted on, and the compound (I) was collected by filtration, and washed with a small amount of cold water. It was recrystallized from water, and obtained 16.3 g. (yield 78%). It had no crystal water and remained as a non-hydrated compound even when exposed to the air for a long time. It has m. p. 170~171° and $[\alpha]_D^{10} = +89.4°$ (c=1.74, ethyl alcohol). Found: N, 6.64%; neut. equiv., 213. Calculated for $C_{10}H_{11}O_4N$: N, 6.70%; neut. equiv., 209.1.

Fischer[5] has described this substance as having one mole of crystal water, m. p. 171° and $[\alpha]_D^{25°} = +84.8°$ (dried substance, c=2.20, alcohol).

O-Methyl-N-formyl-L-tyrosine (II).—The compound (I) (20.9 g.) was dissolved in 4N-sodium hydroxide (50 cc.). The solution was then treated alternately with 4N-sodium hydroxide (10 cc.) and dimethyl sulfate (4.76 cc.) with mechanical stirring, the temperature being held at 30~35° by cooling; the addition was repeated four times in all. Stirring was continued for two hours at room temperature after all of the dimethyl sulfate had been added. The solution was acidified with 8N-nitric acid, and the crystal was collected and recrystallized from water. 20.3 g. was obtained (yield 91%). It had m. p. 152~154° and $[\alpha]_D^{10} = +94.7°$ (c=2.11, alcohol). Found: N, 6.31%; neut. equiv., 226. Calculated for $C_{11}H_{13}O_4N$: N, 6.28%, neut. equiv., 223.1.

The compound (I) was methylated with methyl iodide and sodium hydroxide in the usual way,[1] and the product obtained had m. p. 151~154°, showing correct elementary analysis. But, in this case, the fact that the product contained a small amount of the compound (I) was recognized in the paper chromatogram of the hydrolysate of this product.

O-Methyl-L-tyrosine (III).—The compound (II) (11.2 g.) was hydrolysed with 3N-hydrochloric acid (100 cc.) for 2 hours. The solution was evaporated under reduced pressure, and the concentration was repeated with the addition of water. The residue was dissolved in a small amount of water and neutralized with ammonia. After cooling, the resulting crystal was collected. This was recrystallized from hydrochloric acid and ammonia, and 8.6 g. was obtained (yield 88%). It had m. p. 263~265° (decomp.) and $[\alpha]_D^{10} = -5.7°$ (c=2.02, 3N HCl). Its phenylhydantoic acid had m. p. 176° and $[\alpha]_D^{15} = +127.5$ (c=3.89, alcohol).

Its *p*-toluenesulfonyl derivative had m. p. 66~

(3) N. Izumiya, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **71**, 500 (1950), **72**, 26, 149, 445, 550, 702, 1050 (1951); The result of concerning, 1 (or 3)-benzyl-L-histidine is unpublished.

(4) R. P. Rivers and J. Lerman, *J. Endocrinol.*, **5**, 223 (1948).

(5) E. Fischer, *Ber.*, **40**, 3716 (1907).

(6) J. S. Fruton and H. T. Clarke, *J. Biol. Chem.*, **106**, 667 (1934).

(7) L. D. Behr and H. T. Clarke, *J. Am. Chem. Soc.*, **54**, 1630 (1932).

67° and $[\alpha]_D^{15}=+32.8°$ (c=3.34, alcohol). Found: N, 3.88%. Calculated for $C_{17}H_{19}O_5NS$: N, 4.01%.

The compound (III) was converted into L-tyrosine by the action of hydroiodic acid. The resulting L-tyrosine was confirmed as optically pure, and had $[\alpha]_D^{10}=-11.9$ (c=2.57, 3N HCl).

Behr et al.[7] have reported the compound (III) as having m. p. 264~265° (decomp.) and $[\alpha]_D^{29}=-5.9°$ (2% in N HCl), and its phenylhydantoic acid as having $[\alpha]_D^{21}=+123.6°$ (4% in alcohol). Rivers et al.[4] have reported the compound (III) as having m. p. 259~260° (decomp.) and $[\alpha]_D^{17}=-10.0°$ (2% in N HCl).

[L]-α-Bromo-β-(p-methoxy phenyl) propionic acid (IV).—The compound (III) (0.1 mol.) and potassium bromide (0.35 mol.) were dissolved in 2.5N-sulfuric acid (0.52 mol.). To the mixture was added sodium nitrite (0.16 mol.) in the usual way.[3] The resulting pale yellow crystal was collected, washed with water. Ths yield was 84 %. It had m. p. 85~89° and $[\alpha]_D^{10}=+13.8°$ (c=1.74, alcohol). It became oily when it was recrystallized from alcohol and water. Found: Br, 29.4%. Calculated for $C_{10}H_{11}O_3Br$: Br, 30.8%.

Rivers et al.[4] have reported it as having m. p. 98~99°.

O-Methyl-DL-tyrosine.—The brome acid (IV) (5.18 g.) was dissolved in 60 cc. of ammonia (saturated at 0°) and heated in a sealed tube at 100° for 1 hour. The solution was evaporated to dryness under reduced pressure, and the residue was collected by the aid of a small amount of cold water. It was recrystallized from hydrochloric acid and ammonia, and 3.20 g. was obtained (yield 82%). This had m. p. 285~287° (decomp.) and no rotation. Found: N, 7.24%. Calculated for $C_{10}H_{13}O_3N$: N, 7.18%. Its phenylhydantoic acid had m. p. 192~193° and showed no appreciable rotation. Found: N, 9.07%. Calculated for $C_{17}H^{18}O_4N_2$: N, 8.92%.

Dakin[8] has reported O-methyl-DL-tyrosine as having m. p. 295° (decomp.).

O-Methyl-D-tyrosine.—The bromo acid was dissolved in ammonia in the manner described above and kept at 0° for 7 days. The yield was 79%. It had m.p. 262~263° (decomp.) and $[\alpha]_D^{10}=+5.4°$ (c=2.11, 3N HCl). Its phenylhydantoic acid had m. p. 176° and $[\alpha]_D^{10}=-124.6°$ (c=2.84, alcohol).

O, N-Dimethyl-D-tyrosine (V).—(A) The bromo acid (5.18 g.) was dissolved in 36 cc. of aqueous methylamine (33%) and heated in a sealed tube at 100° for 30 minutes. The solution was concentrated under reduced pressure, and the residue was collected. It was recrystallized from hydrochloric acid and ammonia, and 2.38 g. was obtained (yield 57%). It had m. p. 247~248° (decomp.) and $[\alpha]_D^{10}=-3.9°$ (c=2.02, 3N HCl). Found: N, 6.74%. Calculated for $C_{11}H_{15}O_3N$: N, 6.70%. (B) The bromo acid was treated in the manner described above and kept at 0° for 5 days. The yield was 64%. It had m. p. 247~249° (decomp.) and $[\alpha]_D^{10}=-3.8°$ (c=2.54, 3N HCl). Found: N, 6.77%. Calcd.: N, 6.70%.

D-Surinamine (VI).—(A) The compound (V) (2.09 g.), $[\alpha]_D^{10}=-3.9°$, was dissolved in 20 cc. of hydroiodic acid (saturated at 0°) and warmed in a sealed tube at 70° for 30 minutes. The solution was concentrated under reduced pressure repeatedly by adding some water each time. The residue was dissolved in a small amount of water and neutralized with ammonia. The resulting product was recrystallized from hydrochloric acid and ammonia, and 1.74 g. was obtained (yield 89 %). It had m. p. 273~274° and $[\alpha]_D^{15}=-18.9°$ (c=1.74, 3N HCl). Found: N, 7.07%. Calculated for $C_{10}H_{13}O_3N$: N, 7.18. (B) In the manner described above, D-surinamine was obtained from the compound (V) ($[\alpha]_D^{10}=-3.8°$). It had m. p. 273~275° (decomp.) and $[\alpha]_D^{15}=-19.1$ (c=2.02, 3N HCl).

Fischer et al.[1] have reported L-surinamine as having $[\alpha]_D^{21}=+19.8°$ and Corti[2] as having m. p. 273° (decomp.) and $[\alpha]_D^{19}=+19.1$~19.3.

Rf values of paper chromatography.—The composition of each solvent was as follows:—phenol: water=100:15, collidine:lutidine=2:5 (saturated with water); acetic acid-*n*-butanol:water=1:4:1. The figures denote the volumes. The amino acids were dissolved in N-hydrochloric acid and tested.

Amino acid	Solvent		
	Phenol	Collidine + Lutidine	Acetic acid + Butanol
L-Tyrosine	0.57	0.61	0.60
D-Surinamine	0·83	0.66	0.66
O-Methyl-L-tyrosine	0.77	0.59	0.70
O, N-Dimethyl-D-tyrosine	0.86	0.64	0.78

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(8) H. D. Dakin, *J. Biol. Chem.*, **8**, 20 (1911).